Intensive Care Med (2014) 40:1039–1045
DOI 10.1007/s00134-014-3343-3

EDITORIAL

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Is there a future for tigecycline?

Received: 9 May 2014
Accepted: 13 May 2014
Published online: 29 May 2014

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In 2010 and 2013, the US Food and Drug Administration (FDA) reported an increased risk of mortality associated with tigecycline use in comparison with other drugs in the treatment of serious infections. The analysis used a pooled group of randomized clinical trials including hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP), complicated skin and soft tissue infections (cSSTI), complicated intra-abdominal infections (cIAI), and diabetic foot infections [1, 2]. On the basis of the pooled data analysis, the FDA recommended that alternatives to tigecycline should be considered in patients with severe infections. After the FDA warning several meta-analysis were published; obviously using different methodologies and selecting different studies. Yahav et al. [3] meta-analysis reported statistically higher all-cause 30-day mortality in the tigecycline arms. On the other hand, Cai et al. [4] found no difference in all-cause mortality and drug-related mortality between tigecycline and the comparators, whereas Tasina et al. [5] demonstrated reduced clinical efficacy and increased mortality for tigecycline, but the difference was not statistically significant. The FDA alert has been further jeopardized by two more studies. McGovern et al. [6] performed an all-cause mortality analysis by use of logistic regression and classification and regression tree analyses on study-level and patient-level data in an effort to find a reason for the increase in mortality. Deaths were attributed to infections or underlying co-morbidities and not to tigecycline. Subsequently, Vardakas et al. [7] separately analyzed studies involving infections for which tigecycline has approval and reported no statistical difference in clinical efficacy and no significant increase in mortality. On the other hand, analyzed data from non-approved indications showed that the tigecycline arm was statistically less effective. Finally, meta-analyses of study-level data suggested decreased clinical efficacy as a possible explanation for the demonstrated imbalance in mortality [3, 8].

In their interesting and welcome article published in the current issue of intensive care medicine, Montravers et al. [9] conclude that tigecycline success rates in patients in ICU with severe infections appear comparable to those reported with other antibiotics; the overall success rate was 60 % at the end of treatment, and 53 % 7 days later. Furthermore, they report a survival rate of 85 % at day 28. Historically, clinical trials concerning management of critically ill and particularly ICU-admitted patients with tigecycline are limited. A few large observational studies have been set up to determine the outcomes of ICU tigecycline-treated patients in clinical practice and a recent multicenter European surveillance study encompassing 1,782 patients (56 % from ICU), who

Table 1 Clinical studies of tigecycline encompassing non-approved indications

Type of study (no of patients)	Type of infection (number of patients)	Pathogens	Treatment regimens (number of patients)	Reported outcomes
Schafer et al. [19] Retrospective case series (25)	VAP (19), VAP with BSI (3), BSI (3) (60 % surgical)	MDRAB 30 % TG-IR, 5 % TG-R	TG monotherapy (5) Combination with CRB or COL (20)	Resolution 84 %; microbial eradication 80 %; recurrence in 15.8 % of patients with VAP; emergence of resistance in 1 patient
Swoboda et al. [20] Rretrospective study (70)	Severe sepsis and septic shock cIAI (30), HAP (12) cIAI + HAP (10), BSI (2), UTI (2), SSTI (6), bone and joint (1), unknown (2)	Gram-positive (58) *Stenotrophomonas maltophilia* (13), *Acinetobacter baumannii* (1), *Enterobacter cloacae* (1), *Burkholderia cepacia* (1)	TG monotherapy (1) Combinations with CRB (29), FQ (5), CEP 3rd generation (3), COL (3), AMG (3), VAN (1)	30 % ICU mortality Outcomes of gram-negative infections cannot be separated
Vasilev et al. [21] Phase 3, open-label, prospective, non-comparative study (34 = microbiologically evaluable population)	cSSTI (24) cIAI (5), HAP (5), CAP (1), BSI (1)	*A. baumannii* (17), *Klebsiella pneumoniae* (6), *Escherichia coli* (9), *Enterobacter* spp., (4) No strict MDR definition used	TG monotherapy (34)	Clinical cure 72.2 % Microbiological cure 66.7 % For *A. baumannii* infections clinical cure 82.4 % and microbiological cure 64.7 %
Anthony et al. [22] Retrospective case series (18, 19 infection courses)	VAP (3), VAP with empyema (3), HAP (2), BSI (1), UTI (2), tracheobronchitis (2), mediastinitis with secondary BSI (1), other (4)	10 MDRAB; 44 % TG-S, 56 % TG-IR 6 *K. pneumoniae* (4 ESBL+, 1 ESBL + KPC), 2 *E. cloacae,* 1 *E. coli* (KPC)	TG monotherapy (9) Combinations: CEF (1), AMK + COL (1), inhaled COL (1), TOB (1), inhaled TOB (2), GEN (1), LEV (1), MER + COL (1)	Positive clinical response 50 %, uncertain 10 %, survival 60 %; all deaths related to infection with TG-IR pathogens; microbiological response in 75 %; emergence of resistance in 1 patient
Gallagher and Rouse [23] Retrospective case series (28 patients, 29 courses)	HAP (15), BSI (6, 2 of them with HAP), UTI (3), IAI (1), wound infection (3), tracheobronchitis (1)	29 *A. baumannii*	TG monotherapy (12) Combinations: IMP, COL, AMK, P/T, AMP/S (17 courses)	28 % positive clinical outcome 44 % microbiological eradication 62 % negative outcome, 68 % mortality (19 patients, attributable in 15/19 patients) Clinical and microbiological outcomes associated significantly
Curcio et al. [24] Prospective non-comparative study (75)	VAP (6 with BSI)	*A. baumannii* 44/73 IMP-S, 29/73 only COL-S/TG-S	22 patients no other antibiotics or <48 h (37 % received concomitant antipseudomonal treatment)	69.9 % clinical success Success in 2/6 bacteraemic infections 33 % crude mortality
Gordon and Wareham [25] Retrospective case series (34)	IAI (2), HAP (8), IAI + HAP (1), BSI (2), IAI + VAP (3), BSI + other (7), bone and joint and SSTI (10), intracranial (1)	*A. baumannii* (19), polymicrobial with *A. baumannii* (15)	TG monotherapy (12) Combinations (22)	68 % positive clinical outcome, 29.4 %microbiological eradication, 56 % positive results in bacteraemia Mortality: overall 41 %, attributable 26.4 %; 3 breakthrough BSI (1 with resistance)
Poulakou et al. [26] Retrospective case series (45)	VAP/HCAP (21, 2 with BSI), BSI (10), SI (14)	*A. baumannii* (26 MDR, 2 PDR, all CRB-R) TG MIC 1–8 mg/L, *K. pneumoniae* (20 MDR, 3 PDR), TG MIC 1–3 mg/L, *Enterobacteriaceae* (3)	TG monotherapy (22) Presumed active monotherapy (23: COL 8, CIP 1, MER 1, ATM 1, COL + AMK 3 COL + MER 6, COL + LNZ 1, MER + MTN 1, COL + VAN 1	Clinical success: VAP 90 %, BSI 80 %, SI 64.3 %, monotherapy group 81.8 %, combined therapy group 78.3 %, 4 breakthrough gram-negative BSI (1 with emergence of resistance), 10 superinfections from microorganisms inherently resistant to TG
Jamal et al. [27] Retrospective study, description of 3 institutional outbreaks (24)	HAP/VAP (5), BSI (9), CR-BSI (1), UTI (2), cSSSI (1)	MDRAB [1st outbreak isolates meropenem-susceptible (MIC 2–3 mg/L)]. TG MIC 0.75–2 mg/L	First outbreak: start with combination of CIP + AMG, switch to MER Second and third outbreaks: monotherapy with TG	First outbreak 6 patients, 50 % mortality, time to pathogen clearance 8.3 days Second outbreak: 12 patients, 8.6 % mortality, time to clearance 2.8 days Third outbreak: 6 patients 0 % mortality; time to clearance 3.1 days

Table 1 continued

Type of study (no of patients)	Type of infection (number of patients)	Pathogens	Treatment regimens (number of patients)	Reported outcomes
Freire et al. [28] Phase 3, multicenter, randomized, double-blind study (945)	Non-VAP (27), VAP (40)	67 *A. baumannii* (MIC range 0.12–8 mg/L)	TG plus optional adjunctive therapy with CAZ or IMP and optional adjunctive therapy with VAN An AMG was permitted for double coverage against *P. aeruginosa*	Cure rates 67.9 % for TG and 78.2 % for IMP (CE patients) and 62.7 % and 67.6 % (c-mITT patients), respectively Overall mortality: TG 14.1 %, IMP 12.2 %, although more deaths occurred in VAP patients treated with TG (NS) Overall TG was noninferior to IMP for the c-mITT but not the CE population; this difference appears to have been driven by results in VAP patients For *A. baumannii* infections, clinical response: non-VAP TG 90 % IMP 70.6 %; VAP TG 57.1 % IMP 94.7 %. Eradication of *A. baumannii* at test of cure was 71 %
Metan et al. [29] Retrospective study (21)	SI, VAP	18 *A. baumannii* infections, 3 co-infections with other pathogens	TG monotherapy (7) Combination: various (14)	Clinical success 80.95 % 14-day attributable mortality 9.5 % Crude 30-day mortality 19.1 % SI better outcomes
Kuo et al. [30] Retrospective study (66)	Group 1, FDA-approved indications (12); group 2, HAP (38); group 3, UTI (4), osteomyelitis (4), CRBSI (3), BSI (3), 57.6 % ICU patients	25 patients with MDRAB. The rest of them: *K. pneumoniae Citrobacter* spp., *Serratia* spp., *S. maltophilia.* *P. aeruginosa*, *Providencia stuartii*. Susceptibility to TG is not reported	65.1 % combination therapy Patients with MDRAB: 10 received TG monotherapy and 15 combination therapy (Single combination therapy 13 cases: SUL 6/25, P/T 2/25, CEF 3/25, IMP 2/25)	Positive clinical outcome 30.3 %; higher clinical success rate for group 1 than group 2, which may correlate with higher disease severity and risk factors in group 2 For MDRAB infections, positive clinical outcome 12 %; microbiological eradication in only 1 patient; 18 persistent infections and four superinfections. Hospital mortality 68 % For VAP caused by MDRAB, the success rate was 5.6 %
Ye et al. [31] Retrospective observational study (112)	116 episodes of pneumonia involving *A. baumannii;* 10 patients with bacteremia	Semiquantitative respiratory cultures used. Monomicrobial *A. baumannii* pneumonia in 26.7 %; high rates of polymicrobial pneumonia [73.3 %, 30.2 % of which with gram(+) and 56.7 % with other gram(−) pathogens]	Combination therapy 62.1 % (in descending order CEP, FQ, CRB, AMK, SUL) 31 monomicrobial episodes: 9 received TG monotherapy and 22 combination therapy 85 polymicrobial episodes: 35 TG monotherapy and 50 combination therapy	The episodes with monomicrobial MDRAB pneumonia had a significantly lower clinical resolution rate than polymicrobial episodes (45.2 vs. 65.9 %; no difference with monotherapy. Among 6 episodes with MDR bacteremia only those with tigecycline MIC $\leq$ 1 mg/L survived 30-day mortality was 36.2 %
Guner et al. [32] Retrospective study (33)	VAP (19), BSI (11), SSI (2)	MDRAB or polymicrobial infection involving MDRAB	TG alone, 2 patients; TG + AMG, 22 patients; TG + CFP/SUL, 9 patients	Positive clinical outcome 63.63 % No significant difference between VAP and BSI in terms of clinical or microbiological outcome 30-day overall mortality 57.6 % Attributable mortality 24.2 % Superinfections 39.3 %

Table 1 continued

Type of study (no of patients)	Type of infection (number of patients)	Pathogens	Treatment regimens (number of patients)	Reported outcomes
Ku et al. [33] Retrospective comparative study (106)	CR-BSI (9), HAP/VAP (50), UTI (14), SSTI (22)	82 *A. baumannii,* 12 CRE, and 12 *A. baumannii* + CRE coinfection 82 % of isolates were nonsusceptible to TG	71 patients COL 16 with TG 19 with COL + TG	Patients who received COL alone or COL + TG more likely to die than patients receiving only TG (37 % vs 0 %) Patients receiving COL had higher severity of acute illness and delays in initiation of effective antimicrobial therapy
Moon et al. [34] Retrospective study (108)	HAP (44, including not reported number of VAP cases), SSI (22), cIAI (18), BSI (5), non-ICU population	*A. baumannii* 50.3 % (57/83 CRB-R) *S. aureus* 10.3 %, *K. pneumoniae* 7.9 %, *Enterococcus* spp. 6.7 %, *E. coli* 5.5 %, *P. aeruginosa* 4.9 %	TG monotherapy: 71 cases Combination: CRB 20, AMG 4, GLP 3 cases	Overall 30-day mortality 52.9 % 30-day mortality of HAP 60.5 % 30-day mortality of *Acinetobacter* spp. infection 59.4 % Superinfection: 29.6 % (mostly *P. aeruginosa*)
Kim et al. [35] Retrospective case series (9)	BSI 9 cases (primary BSI, 1 case; CR-BSI, 3 cases; secondary to HAP/VAP, 3 cases; secondary to IAI, 3 cases)	All *A. baumannii* isolates were CRB-R and COL-S, TG-S (TG MICs 0.125–1.0 μg/mL)	TG monotherapy 1 Combinations: CRB 4, CEF 1, MOX + VAN 1, CTZ + LNZ 1, MER + VAN 1	Attributable mortality 55.5 % All-cause hospital mortality 66.7 %
Lee et al. [36] Retrospective comparative study (386)	HAIs not further explained	MDRAB susceptibility rates of TG evaluated by Kirby Bauer	Treatment groups: TG 266 patients non-TG 108 patients TG group: 108 patients treated with TG alone and 158 treated in combination (CEP, P/T, or CRB). Non-TG group: 120 patients (all treated with IMP and SUL)	TG and non-TG groups did not differ significantly in the number of infection-related deaths, length of hospital stay, or length of ICU stay and survival rates. Unfavorable outcomes significantly lower in the TG group than in the non-TG group (30.8 % vs 50 %). The most significant predictors of favorable outcomes: TG treatment and microbial eradication
Ramirez et al. [16] Phase 2 study; safety and efficacy of two higher doses of TG with IMP in HAP (105)	HAP/VAP	8 *A. baumannii*, 15 *Enterobacteriaceae*, 3 *Haemophilus* spp., 23 *S. aureus*	TG 150 mg followed by 75 mg every 12 h or 200 mg followed by 100 mg every 12 h or 1 g of IMP every 8 h Empirical adjunctive therapy could be administered for initial coverage of MRSA and *P. aeruginosa*	Clinical cure with TG 200 mg/day (85.0 %) was numerically higher than with tigecycline 150 mg/day (69.6 %) and IMP (75.0 %) Significant PK/PD clues supportive of the need for high doses to achieve better outcomes in VAP/HAP
Bassetti et al. [10] Observational multicenter registry (1,782)	cSSTI (254), cIAI (785), pneumonia, BSI, sepsis, ICU admission heterogeneous	At least 1 resistant pathogen: cSSTI 30.5 % cIAI 17.5 %	Monotherapy (50.4 %) Combination therapy in descending order (CEP, FQ, CRB, AMG, PEN, COL, MTN, GLP)	Clinical response rates to treatment with TG alone or in combination were: cSSTIs 79.6 % and cIAIs 77.4 % All-cause mortality cSSTI 9.4 %, cIAI 18.7 %
Chuang et al. [37] Retrospective study, comparative (294)	HAP, VAP prospectively monitored	MDRAB Among 104 tested isolates, COL-S 100 % TG-S 50 % Qualitative testing of respiratory secretions	119 COL-based, 175 TG-based Combination in the TG arm 17.14 %; in the COL arm 15.9 %, in descending order: CRB, SUL, AMG	84 pairs of patients entered propensity score Significantly higher mortality rate was found in the TG-based group (60.7 %) vs. the COL group (44 %) Post hoc analysis showed that the mortality difference was noted in those with higher tigecycline MIC (>2 μg/mL)

Table 1 continued

Type of study (no of patients)	Type of infection (number of patients)	Pathogens	Treatment regimens (number of patients)	Reported outcomes
Montravers et al. [9] Prospective, observational multicenter (156)	IAI (56 %), cSSSI (19 %), other (25 %), bacteremia in 12 % Hospital-acquired (89 %), ICU population	Gram(+) cocci 41.2 %, 3.8 % TG- IR/R Gram(−) bacteria 47.2 %, 26 % TG-IR/R Non-fermenting gram(−) 6 %, 50 % IR or R to TG Polymicrobial infection 18.6 %	65 % combination treatment (in descending order: AMG, PEN, FQ, CRB)	Global success rate 60 % at the end of treatment; significantly higher with treatment duration more than 9 days (76 % vs. 47 %) and in patients with BMI $\leq$ 35 kg/m^2 (56 % vs 13 %) Survival rate at day 28, 85 % (significantly higher in the less severely ill patients)

MDRAB multidrug-resistant *Acinetobacter baumannii*, *VAP* ventilator-associated pneumonia, *CAP* community-acquired pneumonia, *HCAP* healthcare-associated pneumonia, *HAP* hospital-acquired pneumonia, *UTI* urinary tract infection, *BSI* bloodstream infection, *CR-BSI* catheter-related BSI, *cIAI* complicated intra-abdominal infection, *cSSTI* complicated skin and soft tissue infection, *SI* surgical infection, *MDR* multidrug resistant, *PDR* pandrug resistant, *MIC* minimal inhibitory concentration, *XDRAB* extensively drug resistant *A. baumannii*, *TG* tigecycline, *COL* colistin, *CRB* carbapenem, *CEP* cephalosporin, *CEF* cefepime, *CAZ* ceftazidime, *CFP/SUL* cefoperazone/sulbactam, *VAN* vancomycin, *MER* meropenem, *IMP* imipenem, *AMG* aminoglycosides, *AMK* amikacin, *GEN* gentamicin, *TOB* tobramycin, *FQ* fluoroquinolone, *LEV* levofloxacin, *CIP* ciprofloxacin, *P/T* piperacillin tazobactam, *AMP/S* ampicillin sulbactam, *MTN* metronidazole, *LNZ* linezolid, *ATM* aztreonam, *PEN* penicillins, *CRE* carbapenem-resistant *Enterobacteriaceae*, *S* susceptible, *IR* intermediately resistant, *R* resistant, *ESBL* extended spectrum beta-lactamase, *KPC* carbapenemase-producing *Klebsiella pneumoniae*, *NS* non-statistically significant, *GLP* glycopeptides, *PEN* penicillins

received tigecycline under real-life conditions of daily clinical practice. In this study tigecycline was used to treat a variety of infections, including some for which tigecycline was not granted approval for use, and the efficacy and safety profile support the use of this drug in complicated infections in critically ill patients [10]. Studies of clinical experience with tigecycline in non-approved indications suffer significant heterogeneity and report a variety of clinical and microbiological endpoints with diverse rates of efficacy and mortality ranging from 12 % to more than 80 %. In the majority of them, the true contribution of tigecycline to the outcome is confounded by the use of various combination regimens. These studies are summarised in Table 1.

Furthermore, recent published reports of infections caused by multidrug-resistant (MDR) pathogens with limited therapeutic options, including bacteria from the ESKAPE group, have highlighted an encouraging role of tigecycline in off-label use as part of a combination regimen. Specifically, tigecycline has been successfully used against life-threatening infections due to carbapenemase-producing *Klebsiella pneumoniae* (KPC) and MDR *Acinetobacter baumannii* in combination with other agents [11, 12]. In a large retrospective multicenter study significant reduction of 30-day mortality was demonstrated by logistic regression analysis when combination therapy (i.e., tigecycline, colistin, and meropenem) was used instead of monotherapy against KPC [12].

Almost 10 years after the launching of tigecycline, microbiological issues still exist. Although considerable in vitro activity has been shown for tigecycline against difficult-to-treat bacteria, the results are not universally consistent and may have varied according to different microbiological breakpoints. Furthermore, Vitek automated systems seem to overestimate resistance to *K. pneumoniae* KPC(+) strains, compared to E-test, therefore discouraging its use in a proportion of infections by almost untreatable pathogens [13]. In vitro interaction synergy studies against KPC or carbapenem-resistant *Acinetobacter* spp. have revealed promising effects of tigecycline in combination [14, 15]. Despite the demonstration of an adequate activity against *Acinetobacter* species of clinical significance [14], the question regarding whether tigecycline constitutes an effective option against resistant *Acinetobacter* spp. has not been comprehensively confirmed.

Another important issue is whether the dosage used so far was adequate from a PK/PD standpoint. A recent phase 2 study in HAP and VAP investigated the use of two high-dosage (HD) tigecycline regimens (200 mg initial, and then 100 mg twice daily or 150 mg initial and then 75 mg twice daily) showing higher cure rates when the "highest" HD was used compared to lower dosage and imipenem/cilastatin

[16]. The study hypothesized that a higher area under the concentration–time divided by the MIC (AUC/MIC ratio) above one was necessary on the basis of a previous phase 3 study demonstrating lower cure rates in patients with HAP treated with conventional dose of tigecycline; this effect was attributed to a lower exposure to the drug on the lung tissue level [16]. This undermines the necessity of high doses when the MIC of the pathogen exceeds 0.5 mg/L. Similarly, another study encompassing 100 ICU patients treated with either standard or HD tigecycline showed no differences in terms of ICU mortality but numerically higher clinical cure rate and microbiological eradication in the HD arm compared to the tigecycline standard dose group. In the multivariate model HD tigecycline was a predictor of clinical cure [36]. Furthermore, compared to colistin that did not reach sufficient drug levels in the lung tissue, HD tigecycline was efficacious for treating experimental pneumonia due to metallo-beta-lactamase (NDM-1)-producing *Enterobacteriaceae* [17].

Although no major issues of toxicity have been displayed at high doses so far, the tolerability of these regimens in large trials still needs to be assessed [16]. Finally, tigecycline's propensity to select for resistant strains (e.g., MDR *Acinetobacter* spp.) and to induce *Pseudomonas aeruginosa* or *Proteus* spp. superinfections requires further investigation.

In conclusion, despite the obscure vision provided by an impressive number of meta-analyses, tigecycline is expected to be used more often in approved indications and in off-label combination regimens for the treatment of MDR gram-negative infections in routine clinical practice. This is greatly supported by the large observational studies from five European countries and by the Montravers study mentioned above [9, 10]. Well-controlled prospective studies are necessary to evaluate tigecycline's efficacy and safety profile at high doses.

The increased medical need represented by the growing impact of multiresistant infections and the current lack of alternative or new antibiotics suggests that tigecycline benefit–risk continues to be positive.

Conflicts of interest MB serves on scientific advisory boards and has received funding for travel or speaker honoraria from Pfizer Inc. The other authors declare no conflict of interest.

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